Peer Review File

Reviewer A

Comment 1: This is a thought provoking and interesting paper focusing on key issues. However, I feel that the key messages and implications have been missed. For example, this study could be key in awareness campaigns, yet no mention of this is made. The lower numbers of females diagnosed compared to males is a crucial finding which is not explored.

Reply 1: Thank you very much for the positive input on our paper. Following your comments, we have included in the conclusions the importance of using this information in awareness campaigns. Regarding the low number of females included, this is a result of tobacco epidemiology in Spain, where women started smoking much later than men and also later than in other countries such as US or UK. We therefore have not included any comment on this.

Changes in the text: We have included the following sentence in the last paragraph of the manuscript "These results might be included in awareness campaigns and the thought that men have more or different symptoms at diagnosis than women should be disregarded"

Comment 2: Despite a significant P value, the variation in presentation with Pain has not been explored.

Reply 2: Thank you for this comment. We only observed two significant p-values regarding pain. The first was for stage I NSCLC, where 10% of men compared to 17.5% of women reported pain. The second result was for extended SCLC where 33.1% of men reported pain versus 26.1% of women. It can be observed that despite significant, the differences in percentage were low. The difference for SCLC is already commented in the discussion.

Changes in the text: We have introduced this sentence in the second paragraph of the discussion "10% of men compared to 17.5% of women reported pain in stage I patients, and this result was statistically significant. We have not found studying this aspect, which should be further explored."

Comment 3: Smoking status is a key issue in diagnosis but looking at the data the main points coming through are missing from the discussion and results. For example cough is not discussed but the lower levels of cough in male smokers is really important and raises questions around if smokers (particularly males) are aware of changes in cough or if attribute them to smoking rather than lung cancer.

Reply 3: Thank you for this relevant point. We do agree that smoking information is very relevant, but the main focus on the paper was to compare men and women characteristics at diagnosis and not putting emphasis on tobacco consumption. Please note that smoking was

more frequent in men compared to women. While 4% of men were never smokers, 33% of women were never smokers. Regarding cough, the frequency of this symptom hardly varied for women across smoking categories (36.6% to 25.2%). This difference was higher for men, from 29.2% in never smokers to 22.8% in current smokers. We do agree with the reviewer's comment that maybe current smokers can confound cough as a symptom for lung cancer with the classical "smoker cough", making difficult an earlier diagnosis based on this symptom. Nevertheless, we have included some comments in the results and also in the discussion sections.

Changes in the text: We have introduced the following sentence in the last paragraph of the results "Of note the frequency of cough was practically the same across all smoking categories for women but was less frequent for men who were current smokers (22.8%) compared to never smokers (29.2%)". We have introduced the following sentence in the discussion section "It is striking the difference observed for the presence of cough in men, which decreased as smoking consumption increased (22.8% for current smokers and 29.2% for never smokers). Perhaps this is due because smokers are less aware as cough as a symptom of lung cancer and attribute it to the so-called "smoker cough".

Comment 4: No mention of comorbidities, frequency or variation on sex is mentioned but this may have a potential impact on findings.

Reply 4: This study did not include comorbidities such as previous cancers (all cases were incident lung cancer cases). Regarding other comorbidities, we did not collect information regarding the main comorbidities in the age of lung cancer diagnosis such as diabetes or heart failure. We do not have diagnostic confirmation on COPD, which is related with lung cancer onset. Therefore while we have information regarding COPD this was communicated by patients and many of them did not have information on the spirometric values in their clinical records.

Changes in the text: we have included that not having accurate information regarding COPD is a study limitation, though this was not the main objective of the study. We have included this issue in the limitations paragraph (discussion section).

Comment 5: You may also wish to consider focusing this paper on NSCLC rather than the combination.

Reply 5: We have presented results separately by NSCLC (Table 4) and SCLC (Table 3), and these results are commented separately in the results and discussion sections.

Changes in the text: No changes are needed. This information is presented.

Comment 6: Although largely well written there are a couple of typos/unclear sentences - for example there is a duplicate sentence in the abstract.

Reply 6: Thank you very much. We have reviewed the text and have corrected/amended/deleted all typos and mistakes.

Changes in the text: different minor modifications and edition.

The study is designed to: Explore potential sex differences in cancer symptoms at diagnosis of lung cancer

The study design starts with a description of the history of the Thoracic Tumor Registry (TTR). The establishment of a nationwide registry is praiseworthy and important.

The ethical aspect is enclosed and discussed in the MS.

The data collection and variables are thorough and exact explained, and consist in my opinion of relevance to the research question.

Reply to the four previous points: Thank you very much for your positive comments on our manuscript. We also are of the opinion that the study is relevant in the topic.

Changes in the text: Not needed.

Comment: The statistical methods are probably feasible, but I cannot find any adjustment for confounding factors or regression analysis. The study design is a retrospective analysis of the data. The results are presented in multiple tables and figures reporting sex differences (or the lack of differences) in the Spanish lung cancer population at the time of diagnosis.

Reply: Thank you for your comment. It is true that we did not perform any regression analysis. Since our intention was to compare lung cancer characteristics at diagnosis by gender, such regressions are not useful in this case. We have provided statistical comparison between men and women for various different lung cancer characteristics and also taking into account separately non-small cell lung cancer and small cell lung cancer. By the way, the corresponding author has strong skills in biostatistics and epidemiology and the statistical analysis is appropriate for the design and objectives proposed.

Changes in the text: none.

I have some comments and questions I would like to be answered by the authors.

1.   In the Abstract you repeat one sentence twice, lines 57-59. Please correct.

Reply 1: Apologies for the mistake. This has been corrected.

Changes in the text: duplicate sentence has been deleted.

2. The description of the history of the establishment of the registry is to an international audience not interesting and may be erased. Further, a nationwide registry have to be multicentrical, unless the country is very, very small with only one hospital (line 123, page 3).

Reply 2: Thank you. This registry was multicentric, with more than 80 hospitals taking part and recruiting patients.

Changes in the text: We have deleted the history regarding the registry (methods, lines 144 to 149. We have added the text "in different hospitals" in line 125 to reply to the reviewer's comment.

3. The main content of the registry and its variables, the completeness and national coverage of the registry must in my opinion be more complementary described.

Reply 3: Thank you, we have included more information in the methods section. By the way, we have recently analyzed the coincidence of sex and age distribution of lung cancer cases in the registry with two other sources of information: the population cancer registries (covering up to 30% of all Spanish population), and the information contained in the National Statistics Institute. We have observed that sex and age distribution of this registry is practically the same of these two information sources. We have written a paper on this which is currently under consideration.

Changes in the text: We have introduced the following sentences at the end of the second paragraph of the discussion section "We have recently observed that sex and age distribution of the cases contained in the registry is practically the same as that observed for lung cancer cases in the database of the Spanish Cancer Registries (covering up to 30% of Spanish population) and also with the National Statistics Institute from years 2017 to 2020 (paper submitted). This coincidence between the three information sources reinforces the representativeness of the registry."

4. More important to be described is in my opinion the completeness of the registry; is it mandatory for all hospitals to supply data? Are there regional differences? How is the national coverage?

Reply 4: We have partially replied to this comment in the previous reply. If the hospital decides to participate in the registry, it supplies all new lung cancer cases diagnosed from the start of their participation. There are no regional differences since all regions have at least one hospital taking part and Spain has universal healthcare coverage. With more than 75 hospitals taking part in all regions, the national coverage is high. We have estimated that approximately 10% of all lung cancer cases diagnosed in Spain are included in the registry each year.

Changes in the text: We have introduced this sentence in the Methods section (end of third paragraph): "If a hospital decides to participate in the registry, all new lung cancer cases are included. Practically all Spanish regions have a hospital taking part in the registry, and

approximately 10% of all lung cancer cases diagnosed in Spain are included in the registry each year."

5. The participants of the cooperative group are described as mainly oncologists. In my country, the pulmonologists usually diagnose the lung cancer patients, and they are imposed to enter clinical data to the mandatory national registry. Please enlighten me and discuss the advantages and disadvantages of your approach.

Reply 5: this is the same in our country. Pulmonologists diagnose lung cancer using the combination of imaging tests and biological samples through bronchoscopy, or other image-guided procedures. Once the patient is diagnosed, the case is presented in a multidisciplinary tumor committee where clinicians of different specialties are present (pulmonologists, oncologists, radiologists, radiotherapic oncologists and pathologists). It is mandatory that patients are evaluated in this committee and the clinical treatment is decided collectively. Therefore, oncologists are aware of all new lung cancer diagnosis. A limitation may be that in some limited cases the patient is too ill (mainly SCLC) to undergo any treatment and only palliative care is provided. In any case, oncologists at each participating hospital are aware of all new lung cancer cases and therefore are able to recruit patients. The Spanish Lung Cancer Group is mainly composed by oncologists, and there is no such organization in our country organized by pulmonologists. With more than 500 participants from close to 100 Spanish hospitals, the Spanish Lung Cancer Group has the ability to design and execute the present study.

Regarding the registration of information, some clinical information is mandatorily registered but other information is unknown. This is the case of detailed smoking history (age where smoking started, end of smoking period, current smoking status, number of daily cigarettes), and so on. In many times this information is not complete. The registry also includes mandatory information on the occupational history of patients. This is only one example of the usefulness and complementary information provided by this registry, where much additional information apart from usual clinical information is retrieved.

Changes in the text: We are of the opinion that no changes are needed for this comment.

6. I advise the editor to refer the MS to a thorough statistical review. I miss multivariate regression analysis if applicable.

Reply 6: We understand the concern. Nevertheless, the statistical analysis is appropriate given the main objective of this research, which is to compare descriptively the clinical characteristics at diagnosis between men and women. To do this, we do not need a multivariate analysis, since sex cannot be predicted, and this is also the same for other variables analyzed. For the interest of the reviewer, the first author is Professor of Epidemiology, with strong skills in statistics, and has a Master Degree in Statistics in Health Sciences awarded by the Autonomous University of Barcelona. He has published more than 150 papers on lung cancer epidemiology before, with many of them including multivariate

analysis or even more sophisticated statistical models such as generalized additive models, Cox Regression and many others.

Changes in the text: not needed.

7. In your results, you report both mean and median age. Choose one and remove the other from your table, otherwise, it is confusing.

Reply 7: For time-dependent variables, such as age or survival, it is recommended to use mean and median, because sometimes you can have skewed distribution. In this case, mean and median are very similar, son we have deleted the mean from Table 1 on the results.

Changes in the text: Mean age has been deleted from Table 1.

8. Why do you present the figure 1 at all? Is this your main and most interesting results? I am also not sure if I understand the small circles, what do they represent?

Reply 8: With this figure we tried to show if there were differences on the age at diagnosis by gender regarding the smoking status of participants. Therefore, we divide smoking status in three categories (never-smoker, ex-smoker and current smoker), and we show age at diagnoses by gender for each category. The circles represent values which are named "outliers" and are outside the percentile 10 and 90 of the age distribution. We decided to who this figure because it can be observed that never smoking men are diagnosed earlier than women, but the opposite effect is present for ex-smokers and current smokers, where women are diagnosed earlier. Given the lack of bibliography on this specific point, we are of the opinion that this information might be relevant for the readership.

Changes in the text: no changes made.

9. You write in both the results section and in the discussion section that some results did not reach a difference of 10%. More important to know is whether the difference is statistical significant or not.

Reply 9: We partially agree with this comment, but statistical differences are fueled by sample size. This means that you can have one year of difference on the age at diagnosis of lung cancer between men and women and be significant if you have let's say, one million participants of each sex. Nevertheless, the clinical difference is very small. Something different could happen if there is a 15 years difference between them and you have only 50 participants of each sex. This is the reason why we think it is important to emphasize the difference on percentage irrespective on statistical differences. In this line of reasoning there is a statement of the American Statistical Association recommending to abandon the relevance of p-values. You can find it here https://www.amstat.org/asa/files/pdfs/p-valuestatement.pdf. It is particularly important number the statement number 3 "Scientific conclusions and

business or policy decisions should not be based only on whether a p-value passes a specific threshold."

Changes in the text: no changes made

10. Do you have any explanation to why there are only 25% females and 75% males? Is this similar in other, comparable populations?

Reply 10: Thank you for this relevant point. This difference is due to the lung cancer distribution is Spain which reflects tobacco epidemiology in our country. Spanish men started smoking much earlier than women. Women started massively to smoke in the decades of 1980 and 1990, and this is the reason why there are much more lung cancer cases in men compared to women. The same happens with lung cancer deaths. Nevertheless, from 2003 to 2019, lung cancer deaths in women have increased by a 120%.

Changes in the text: we have included this sentence at the beginning of the second paragraph of the discussion section "…and the fact that we have included 25% of women reflects tobacco epidemics in Spain, where women started smoking much later than men."

11. You state that your MS has a series of shortcomings, but lists only two. Where is the series?

Reply 11: We have added a third limitation, please see below

Changes in the text: We have added this limitation to the limitations' paragraph: "A further limitation is that we do not have accurate information regarding the presence of comorbidities such as COPD, since many patients did not have spirometric information on their clinical records to confirm or disregard the real presence of this disease."

12. In the introduction, you refer to data from an US registry. Why do you not instead find national or European studies to support your thesis?

Reply 12: thank you for this point. In the introduction we cite information from an American registry but also from a multinational study on lung cancer survival. Following your advice, we have introduced two new and recent references from GLOBOCAN and from the Spanish Network of Cancer Registries regarding lung cancer epidemiology.

Changes in the text: This text has been introduced in the first paragraph of the introduction. It contains two new references ". In fact, in Europe and also in Spain, lung cancer is the deadliest cancer (2). The number of new lung cancer cases in Spain for 2021 has been estimated in 29,000 (3)".

13. The main objective of the study is to describe potential sex differences in symptoms at diagnosis of lung cancer. The study do not discover any. However, in my experience, many

patients are detected with lung cancer when examined for other illnesses or symptoms, e.g. heart disease. Without symptoms of lung cancer. How many of your patients did not have any lung cancer related symptoms at the time of diagnosis?

Reply 13.1: This is very relevant and we usually call this "incidental findings", when lung cancer is being discovered "accidentally" when exploring other diseases or even when an abdominal CT scan shows a nodule in lower parts of a lung. We really do not have the information of how many patients from our database where discovered "incidentally". What we have is how many of them have symptoms, and we published these results last year (Ruano-Raviña A, Provencio M, Calvo de Juan V, Carcereny E, Moran T, Rodriguez-Abreu D, López-Castro R, Cuadrado Albite E, Guirado M, Gómez González L, Massutí B, Ortega Granados AL, Blasco A, Cobo M, Garcia-Campelo R, Bosch J, Trigo J, Juan Ó, Aguado de la Rosa C, Dómine M, Sala M, Oramas J, Casal-Rubio J, Cerezo S. Lung cancer symptoms at diagnosis: results of a nationwide registry study. ESMO Open. 2020 Nov;5(6):e001021) where we observed that no symptom was present in 59% of patients diagnosed in stage I; 40% of stage I patients presented with at least one symptom, while 27.7% of patients in stage IV had no symptoms at diagnosis. The results for the present study are approximately the same since we use the same database but we have included close to 6,000 more patients.

Changes in the text: not needed.

13.2. Further and more interesting to know is; how many of your patients would have been detected in a lung cancer-screening program? Your data may be more than sufficient to explore the usefulness of screening in a registry of considerable size with nationwide coverage. The screening programs do differentiate between females and males. Here you may bring new, and important knowledge based on your registry.

Reply 13.2: Thank you for this recommendation. This is the focus of a new study which we are working on. We decided to center the attention in the present study on sex differences and we are of the opinion that if we include more information (i.e. on the topic you suggest), the main message of the current results would be diluted. In a new study, we aim to know (with the patients available), how many patients fulfil lung cancer screening inclusion criteria, and the percentage of patients excluded for different reasons (i.e. years of ex-smokers), not achieving 20 pack-years (current standard in the US), or having an age below 50 or 80 years. In fact, new studies are suggesting that only 50% of lung cancer cases detected in British cohorts fulfil lung cancer screening criteria (Robbins HA, Alcala K, Swerdlow AJ, Schoemaker MJ, Wareham N, Travis RC, Crosbie PAJ, Callister M, Baldwin DR, Landy R, Johansson M. Comparative performance of lung cancer risk models to define lung screening eligibility in the United Kingdom. Br J Cancer. 2021 Jun;124(12):2026-2034).

Changes in the text: no changes needed.

13.3. After a thorough examination of the MS, I find it unfinished. However, it has potential of being restructured to better point out the lack of sex differences. I would only recommend

the MS for publication after a major revision and restructuring. Especially, the everyday use of the results in the clinical practice must be emphasized. As the authors state in the last section of the Discussion: "In our opinion, these results are relevant since they clearly show that the clinical approach to symptom- based lung cancer diagnosis should not be different by sex." (p. 7, lines 309-311). I do not know how the clinical approach to lung cancer is in Spain; do clinicians approach females and males different? If so, this is not explained in the MS.

Reply to 13.3: Thank you very much for your thorough review on our manuscript, which undoubtedly will improve its quality. We have performed many changes into the text, following your comments and also the comments of other reviewer and Editor. In our opinion, the manuscript content has been importantly improved and reply the main objective we had, which was to ascertain if there were or not differences between sex at lung cancer diagnosis. We have observed that these differences seem to not exist, and we have been also able to analyze if there were differences for the most relevant lung cancer classifications (NSCLC and SCLC) and even by smoking status. This approach has not been performed before, and we have the really relevant advantage of our sample size.
In Spain the clinicians approach males and females in the same way, particularly when they are introduced in the quick pathways for lung cancer diagnosis. The problem is probably related with primary healthcare practitioners (this is a personal view), which probably still think that lung cancer is mainly a disease of men.

Changes in the text: No changes performed.